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Case Report

Transient MR changes and symptomatic epilepsy following gamma knife treatment of a residual GH-secreting pituitary adenoma in the cavernous sinus

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Summary

Objective. To report a rare side effect of gamma knife treatment of pituitary macroadenoma.

Case report. In a forty-one-year old female patient acromegaly was diagnosed due to a growth hormone secreting pituitary macroadenoma. Following transsphenoidal surgery the patient underwent gamma knife treatment for persistent uncontrolled acromegaly activity of residual tumor, infiltrating the left cavernous sinus. 15 months later, complex partial seizures were diagnosed and 17 months after gamma knife treatment a gadolinium enhancing lesion was detected in her left medial temporal lobe. Radiation induced changes, radiation necrosis or a glioma were considered. Neuropsychological testing indicated potentially significant post-surgical deficits. Therefore, surgical action was postponed and anti-epileptic treatment was started. Four months later she was free of seizures and an MR scan showed an almost complete regression of the gadolinium enhancing lesion, indicating that it had been due to radiation induced changes.

Conclusion. Gamma knife surgery of a pituitary adenoma may cause radiation induced MR changes of the mesial temporal lobe mimicking glioma or radionecrosis and cause symptomatic epileptic seizures. The awareness of this rare complication is important to avoid unnecessary and potentially harmful diagnostic or therapeutic interventions.

Keywords: Gamma knife; pituitary adenoma; temporal lobe requires.

Introduction

Acromegaly is a rare but serious disorder due to a growth hormone (GH)-producing pituitary adenoma. Retrospective studies indicate that mortality is approximately doubled relative to the general population, mostly due to cardiovascular events [1–3].

Patients with epilepsy suffer from diminished quality of life and have a mortality rate, which has been estimated to be 2–3 times higher compared with the general population [4] and similar to acromegalic patients. Specifically, mortality has been shown to be positively correlated with seizure rate [5]. Therefore, the aim of treatment of patients with epilepsy is to render them seizure free, which is achieved in approximately two thirds by antiepileptic drugs. However, in certain epilepsy syndromes, and in particular in patients with mesial temporal lobe epilepsy (MTLE) pharmaco-resistance is frequent [6]. If additional investigations localize the epileptogenic zone to a brain area that can be removed without serious neurological deficits, surgical treatment should be considered [7]. Patients with temporal lobe epilepsy have been shown to become free of disabling seizures in approximately two thirds following selective amygdalohippocampectomy [8]. Recent evidence suggests that gamma knife surgery can be a therapeutic tool for uncontrolled growth hormone secreting pituitary adenoma and for mesial temporal lobe epilepsy [9, 10]. Radiation induced MR changes outside the radiosurgical target and associated transient increase of seizure rate are well-known side effects of gamma knife radiosurgery for temporal lobe epilepsy. However, these complications have not been reported in larger series of gamma knife treatments for pituitary adenoma [11–13]. In this case report, we present a patient who suffered from delayed

radiation induced MR changes of the mesial temporal lobe and transient symptomatic complex partial seizures following gamma knife radiosurgery of residual pituitary adenoma mimicking a glioma on MR scans.

Case report

The patient is a 41-year-old right-handed female, who signed informed consent allowing us to report the results of her clinical investigations for scientific publication.

In 1999 the patient realized that her fingers and feet were growing and she had to buy new shoes every six months. At the beginning of 2002 symptomatic right-sided carpal tunnel syndrome was diagnosed and treated conservatively. She started to suffer from a new kind of retroorbital headache and was often sweating excessively. In addition, the upper part of her visual fields started to become constricted. Chronic fatigue and snoring was reported and sleep apnea syndrome was suspected. The pneumologist suspected a growth hormone (GH) secreting tumor and referred the patient for endocrinological assessment. Symptoms and signs of acromegaly were recorded and biochemical investigation confirmed a GH-secreting tumor. Perimetry confirmed slightly constricted visual fields bilaterally in the upper nasal quadrants. MR imaging demonstrated a pituitary macroadenoma, which slightly compressed the optic chiasm and infiltrated the left cavernous sinus. Transseptal and transsphenoidal surgery was performed. Histologically the tumor stained mainly for GH with a relatively high proliferation activity (MIB-1-labelling index >3%). Although clinical symptoms and signs of acromegaly improved, biochemical assessment revealed persistent signs and symptoms of acromegaly and MR imaging showed residual tumor in the left cavernous sinus within a distance of approximately 6–7 mm to the optic nerve. In May 2003 the patient underwent gamma knife treatment for the residual adenoma, which was performed by one of us (TM). At the time of gamma knife treatment, the residual adenoma had a tumor volume of 1.5 ccm (Fig. 1). On the day of the treatment, a Leksell stereotactic frame was attached to the patient's head under local anaesthesia and a stereotactic CT scan and MRI were obtained. MRI distortions were corrected for with the CT scan. The tumor was treated with a prescription dose of 30 Gy at the 50% isodose and the tumor margin and a reference dose of 60 Gy to the target center (Fig. 2). The treatment was performed with 7 isocenters of which 6 had a diameter of 8 mm and 1 of 4 mm. The 8 mm collimators had 82 plugs for each shot and the 4 mm collimator had 14 plugs. The target volume was 1.5 ccm, the overall volume of the 10 Gy isodose was 15.1 ccm. Of the mesial temporal lobe, 3.9 ccm were exposed to $\geq$10 Gy and 0.17 ccm to $\geq$24 Gy.

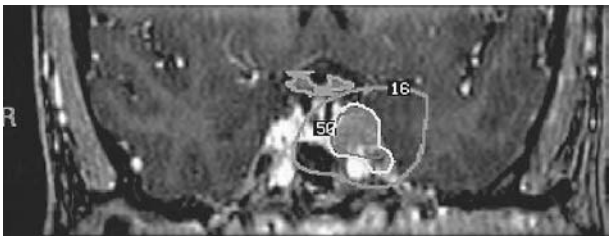

Fig. 2. MR scan showing the treatment plan for gamma knife radiosurgery. The optic chiasm is outlined in blue, the adenoma in red, the 50% isodose in yellow and the 16% isodose in green. The yellow 50% isodose represents the 30 Gy isodose and the green 16% isodose represents the 10 Gy isodose

The treatment course was uneventful and the patient was discharged home the same day. In the following days, starting on the next day, the patient began to experience up to 30 paroxysmal and stereotypical attacks per week consisting of repetitive twitching of the right corner of her mouth and her right arm without impaired consciousness. Focal motor seizures were suspected. A MR scan in July 2003 did not reveal any new pathological findings (Fig. 3) and antiepileptic treatment was not initiated because seizure rate subsequently had decreased to one every other week. Biochemically, IGF-I levels decreased but remained slightly above normal range and, therefore, Sandostatin LAR 10 mg

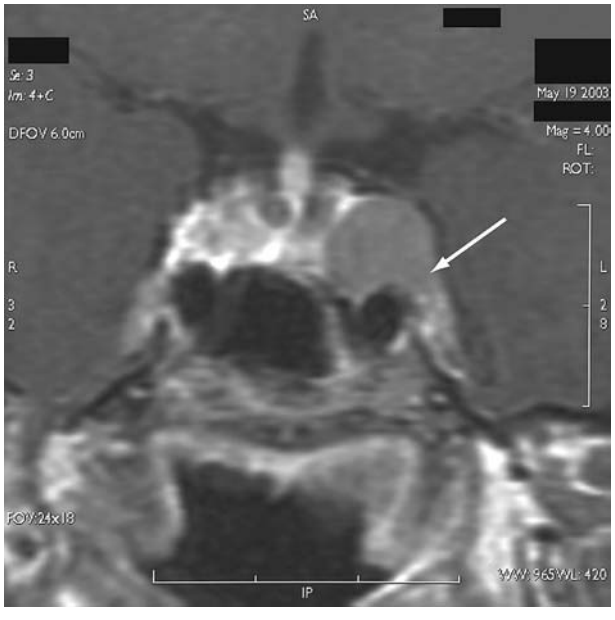

Fig. 1. MR (T1-weighted) scan showing the residual hypophyseal adenoma before gamma knife surgery. The adenoma infiltrates the left cavernous sinus (arrow). The volume of the adenoma was computed to be 1.5 ccm

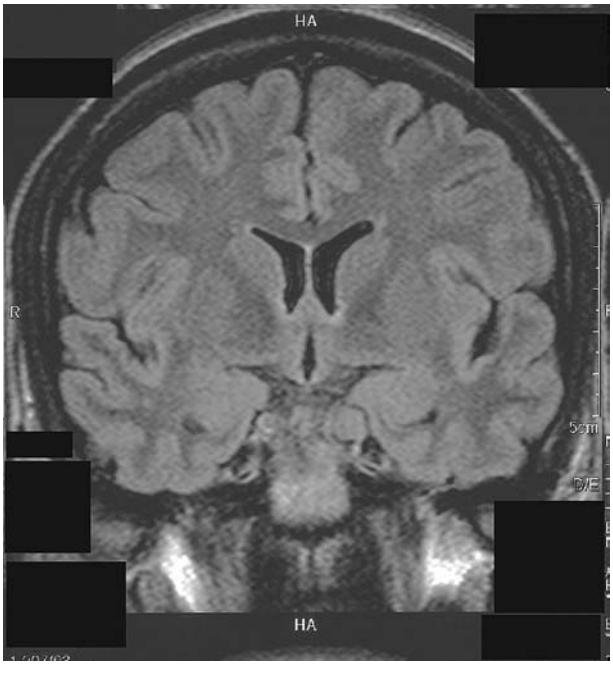

Fig. 3. An MR (FLAIR) scan four months after gamma knife surgery shows the residual hypophyseal adenoma, but no new pathological lesions

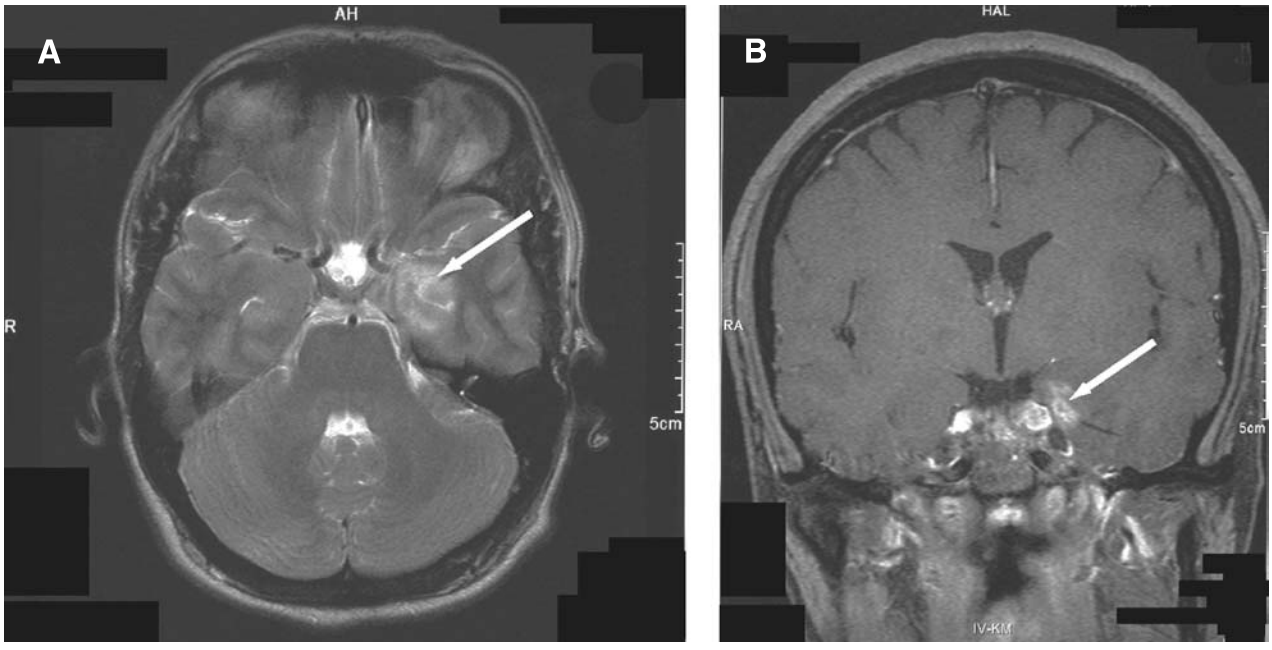

Fig. 4. MR scans 19 months after gamma knife surgery. The T2-weighted image in 3A shows a diffuse signal hyperintensity in the left medial temporal lobe. This lesion enhances after gadolinium as displayed in 3B. The primary differential diagnosis was between low-grade glioma and radiation induced changes or necrosis

every three weeks was initiated with normalization of IGF-I levels. At this time the focal motor seizures ceased. However, in August 2004 a new kind of paroxysmal attacks occurred characterized by 'a peculiar and rather unpleasant sensation' in the patient's head, which was followed by a 'strange feeling of familiarity', evolving into impairment of consciousness. Postictally the patient was extremely tired for several hours and suffered from speech problems, which only slowly resolved. These attacks could occur up to eight times per day. MR imaging in October 2004 revealed a space occupying lesion in the medial left temporal lobe, which showed central enhancement in the uncus and in the parahippocampal gyrus (Fig. 4). The paroxysmal attacks were diagnosed as symptomatic complex partial seizures. EEG showed intermittent slowing over the left fronto-temporal region but no epileptiform activity. Carbamazepine was started but seizure rate continued to increase.

The differential diagnosis basically consisted of a new brain tumor, primarily a glioma or radio-surgery induced changes or necrosis. An irradiation induced neoplasia seemed unlikely given the short time period following irradiation [14]. Surgical exploration was recommended. However, the patient asked for a second opinion and was transferred to our hospital in November 2004. MR scans were repeated and showed progression of the lesion in the temporal lobe, which appeared centrally necrotic (Fig. 5). A 2-[18F]-2-deoxy-D-glucose (FDG)-PET of the brain

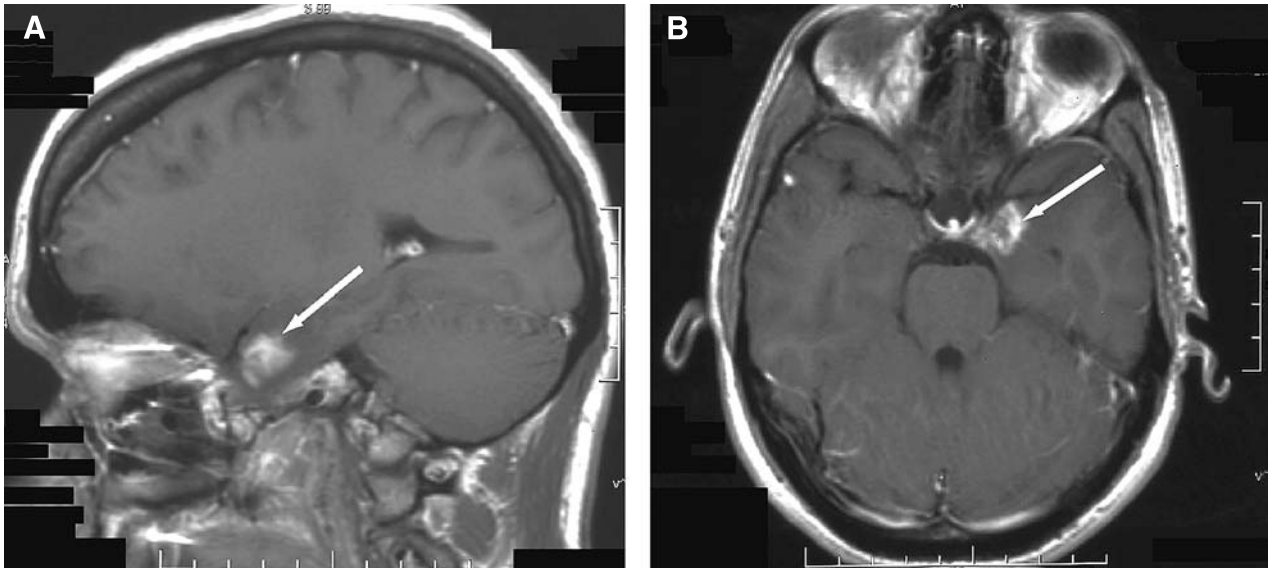

Fig. 5. Gadolinium enhancement in the left medial temporal lobe was slightly progressive 20 months after gamma knife surgery as shown (arrows)

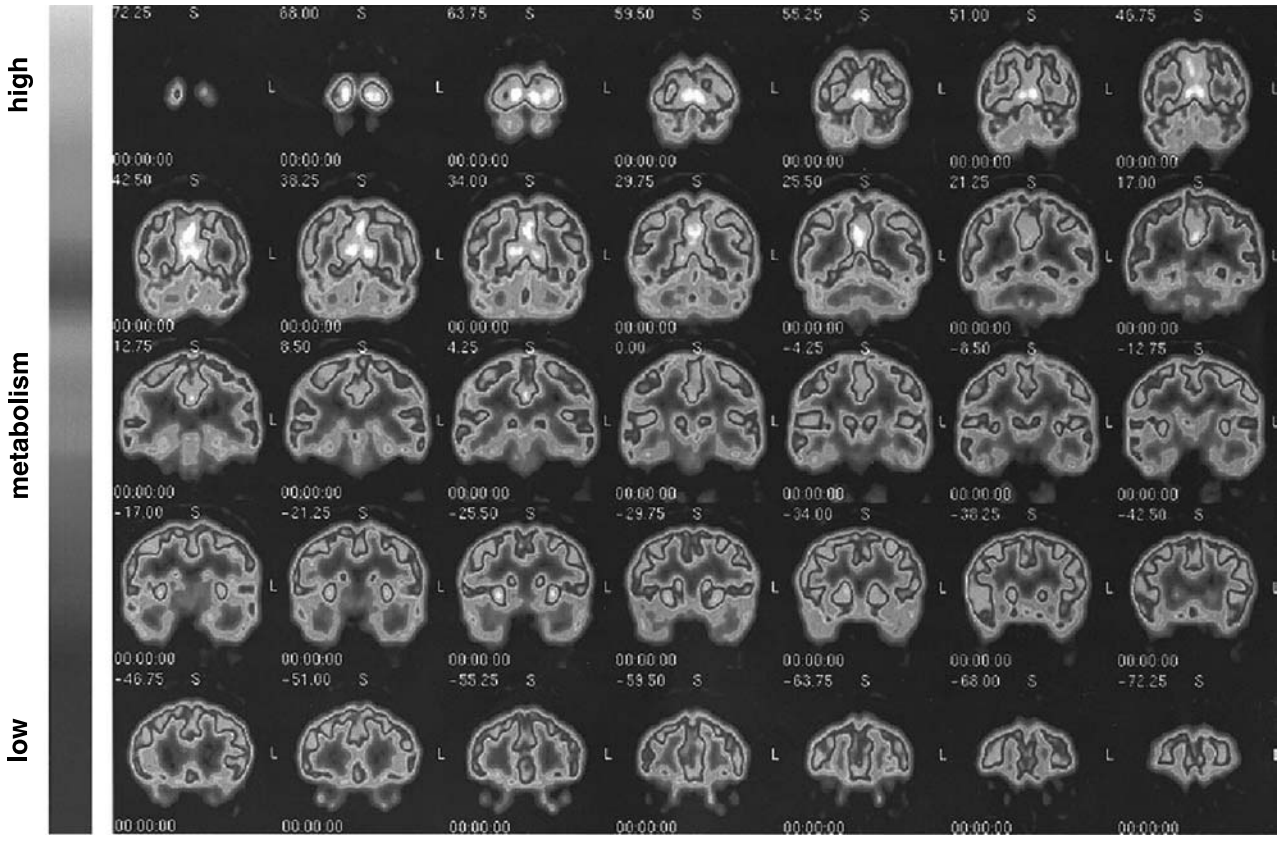

Fig. 6. 18F-FDG-PET 20 months after gamma knife surgery scan detected no significant asymmetries and specifically no regions of asymmetrical hypometabolism in the temporal lobes as would be typical for radio necrosis. Low metabolism is coded by dark blue to black colors as indicated by the color bar on the left

is displayed in Fig. 6 and did not show any significant regions of asymmetric hypometabolism. Magnetic resonance spectroscopy (MRS) was performed and demonstrated increased N-acetylaspartate- (NAA-) and choline peaks in the pathologically altered lesion compared to normally appearing brain tissue. No lipids were detected in the lesion by MRS. These findings were considered to support the diagnosis of a glioma.

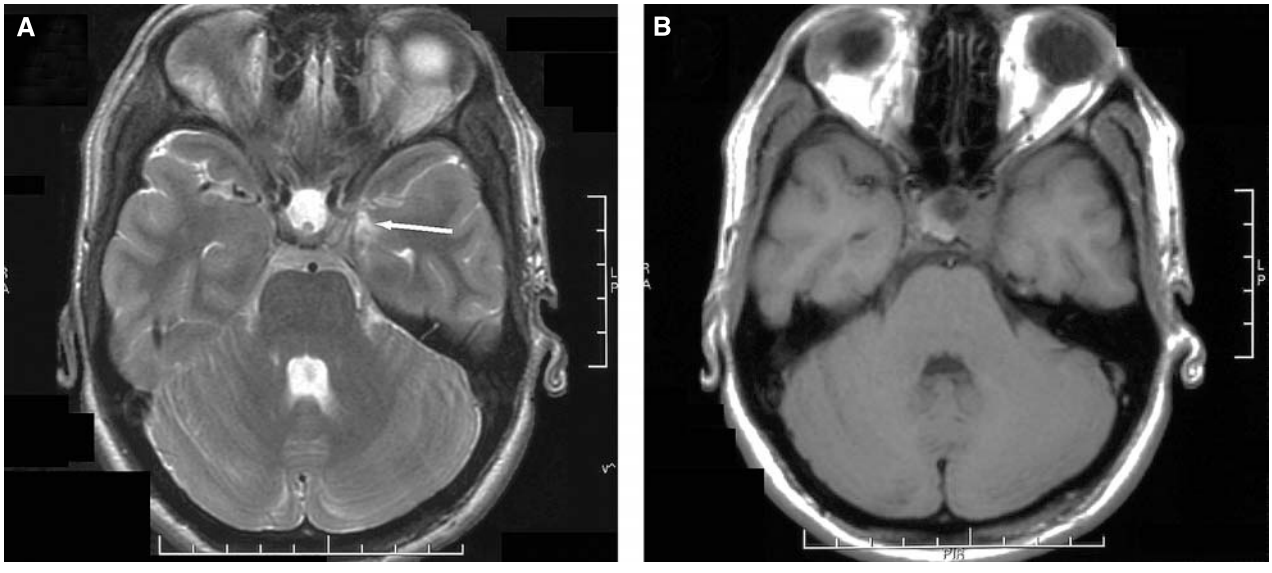

Fig. 7. MR scan 25 months after gamma knife surgery. The T2-weighted image in A shows a regressive lesion in the left medial temporal lobe with only minimal remaining signal hyperintensity (arrow). The T1 weighted image in B reveals no structural changes in the left temporal lobe. The residual hypophyseal adenoma is reduced in size compared to earlier imaging studies

Further pre-surgical evaluation was performed using a selective Wada-test with inactivation of the territory of the A. choroidea anterior on the left side [15]. The neuropsychological results indicated high probability for impairment of memory and language deficits after surgical removal of the lesion. It was, therefore, decided to postpone surgical procedures. In January 2005 the epileptic seizures ceased under continuing medication with carbamazepine. A MR scan was repeated in April 2005 and revealed a significant regression of the lesion in the temporal lobe (Fig. 7). On the follow-up visit in July 2005, the patient had remained seizure-free. In August 2005, IGF-1 and oral glucose suppression test were within normal limits without octreotide medication. Two years and three months after gamma knife radiosurgery, the acromegaly was controlled.

Discussion

We present the case of a successful treatment of acromegaly resulting from residual parasellar GH-secreting pituitary adenoma in the left cavernous sinus with gamma knife radiosurgery. As a side effect of the treatment, the patient however developed transient radiation induced MR changes of the adjacent left mesial temporal lobe with transient complex partial seizures. In order to treat patients with pharmaco-resistant temporal lobe epilepsy, Régis *et al.* [10] used the Leksell gamma knife in 21 patients. They targeted the mesial temporal lobe structures such as the anterior parahippocampal cortex, the basal and lateral part of the amygdala and the anterior hippocampus with a prescription dose of 24 ± 1 Gy at the 50% isodose and the target's margin and a reference dose of 48 Gy. The target volume in radiosurgery for amygdalohippocampectomy typically ranges from 5–8 ccm, which means that 5–8 ccm of mesial temporal lobe tissue are exposed to $\geq$24 Gy. Accordingly, during surgical amygdalohippocampectomy typically 8 ccm of mesial temporal lobe tissue are removed. In comparison, in our patient 0.17 ccm of the left mesial temporal lobe received $\geq$24 Gy during gamma knife radiosurgery and 3.9 ccm of the mesial temoral lobe were exposed to $\geq$10 Gy. In the patient group of Régis *et al.*, the peak of MR changes appeared in the mesial temporal lobe with a median delay of 13 months after gamma knife treatment (mean: 15; range 8–21 months). The median duration of this peak was 53 days (mean: 55; range 31–111 days) and 62% of the patients were prescribed corticosteroids during this time. In our case, the first significant MR changes were detected 17 months after gamma knife treatment and were seen to be clearly regressive on follow-up MR scan 6 months later, in keeping with the observations of Régis *et al.* [10]. Importantly, in some patients with temporal lobe epilepsy radiosurgery resulted in a transitory increase in seizure rate and improvement of the seizure condition occurred between 12–18 months following gamma knife therapy. In the 21 patients reported by Régis *et al.* [10] the average number of seizures per month decreased from 10.1 pre-operatively to 7.3 one week later, but re-increased to 9.3 on follow up visit I (6 months) before it started to continuously drop and finally reach 1.5 after 2 years. In our patient the complex-partial seizures typical of medial temporal lobe onset started 15 months following gamma knife surgery and were controlled approximately four months later by carbamazepine. This time course may be explained by the fact that radio-induced changes occurred in brain parenchyma that was not epileptogenic before treatment as compared to the patients of Régis *et al.* [10]. Thus, the epileptogenic changes had first to take place, which may explain the slightly delayed seizure onset. Furthermore, the primary target of radiotherapy in our patient was not the temporal lobe but the residual adenoma, which infiltrated the left cavernous sinus.

MR scan, FDG-PET and MRS were consistent with the diagnosis of a glioma. Though there are reports of spontaneous regression of low-grade astrocytoma [16] especially in patients suffering from neurofibromatosis type 1, spontaneous regression of malignant glioma was only reported after subarachnoid hemorrhage thereby inducing vasospasm and probably compromising the blood supply of the tumor [17]. The regression of the malignant glioma was only temporary and the patient eventually died a few years later. In the present case, the patient was not known for neurofibromatosis and subarachnoidal haemorrhage was never detected favoring the diagnosis of radiation induced changes in the temporal lobe. It is intriguing that the FDG- PET scan did not detect localized hypometabolism in the left temporal lobe as would be typical for radiation induced necrosis [18]. One theoretically possible explanation for these PET findings could be that there was intensive though still subclinical epileptogenic activity taking place at the time of the PET scan, which compensated for any existing radiation induced hypometabolism in this region. Furthermore, the MR spectroscopy detected an increased NAA peak relative to the contralateral side [19] pointing to an increased cellular density as often observed in gliomas. Whether radiation induced inflammation might explain these MRS findings remains speculative, too.

To our knowledge, we report the first case of radiation induced changes of mesial temporal lobe structures and transient symptomatic epileptic seizures as a rare side-effect of gamma knife radiosurgery of a pituitary adenoma. Radiosurgery induced changes may mimic malignant glioma and the knowledge of the typical clinical

course of radiation induced temporal lobe changes is very important to prevent potentially harmful diagnostic and therapeutic interventions. It is therefore important that a neurosurgeon who performs radiosurgery is involved in the follow-up of the patient. The question arises if an alternative radiosurgical treatment e.g. with a dedicated multimicroleaf collimator linear accelerator (LINAC) may be less probable to lead to this side effect. This is unlikely since the radiation dose to brain tissue outside the target volume is significantly higher in the treatment of skull base tumors with the LINAC than with the gamma knife [20].

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Comment

This is an interesting and well-written report regarding a rare complication of gamma knife surgery. The case they present had residual tumour invading the cavernous sinus. High dose radiation, required to achieve endocrine control, resulted in transient radiological changes in the mesial temporal structures, associated with seizures.

This paper raises a few important issues. First, it is of note that such complication can arise, despite the high precision of radiosurgery. If high doses have to be used, the penumbra may be exposed to sufficient radiation dose to cause untoward changes. In this case the dose applied was indeed near the upper limit of what one would use and perhaps for such a large tumour this may not be the level used in other centres. It is true to say however that in order to ensure endocrine control it is not unusual to use 30 Gy peripheral dose. Size of the tumour was important in this case also because it resulted in a kind of dose plan which avoided the optic pathways but the maneuvers necessary for this resulted in higher dose within the temporal lobe than usual.

Second, the authors rightly indicated that the changes were temporary. It is indeed the experience with many radiologically frightening MR changes, that they resolve in a predictable timeframe. This is particularly important when the treatment was delivered for benign conditions, for instance for the treatment of mesial temporal sclerosis. Anxiety during the period when these changes are prominent leads to investigations, at times even biopsy or resection. Noninvasive investigation, like the MR spectroscopy in this case, may be misleading, suggesting a glioma, and it may be at times difficult to resist surgical intervention. In this case it was only the Wada test, suggesting high risk after resection, that prevented this happening.

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